

18 Evolutionary Developmental Biology

Evolutionary developmental biology is an emerging new research area that explores the links between two fundamental processes of life: development of individual organisms (ontogeny) and evolutionary transformation in the course of the history of life (phylogeny). For some of its more ardent proponents evolutionary developmental biology, or *evo-devo* for short, represents a new paradigm that completes the “Modern Synthesis” of the 1930s and 1940s, while others, often those with a more astute sense of the history of biology, have emphasized the long-standing connections between these two areas of study. But all agree that *evo-devo* offers some of the most promising theoretical perspectives in evolutionary biology at the beginning of the twenty-first century (see for example Amundson 2005, Carroll 2005, Carroll et al. 2005, Hall 1998, Kirschner and Gerhart 2005, Laubichler 2005, Müller 2005, Wagner et al. 2000). In this essay I will first sketch the emergence of present-day evolutionary developmental biology during the last decades of the twentieth century followed by a brief overview of the central questions and research programs of *evo-devo*. I will conclude with a discussion of the one problem – the issue of how to explain evolutionary innovations and novelties – that has the most profound implications for the philosophy of biology. As this example illustrates, the theoretical promise of *evo-devo* lies in the integration of different explanatory paradigms, those of evolutionary biology and population genetics, which are based on the analysis of ultimate causes in the sense of Ernst Mayr, and of developmental genetics and physiology, which attempt to give a mechanistic account of the origins of organismal structures in form of proximate causes, that is, of molecular and cellular mechanisms (Mayr 1961). As we will see,

such integration is not possible without first overcoming serious conceptual and theoretical difficulties. Therefore it should become clear in the course of this essay that any future synthesis of evo-devo will be conceptual rather than simply data driven.

The concept of regulation has, somewhat surprisingly perhaps, emerged as a central topic in evo-devo (see, e.g., Carroll 2005 and Carroll et al. 2005). The idea of developmental regulation has, of course, a long history dating back to early conceptions of the organism as a self-regulating individual, of regeneration and the maintenance of a *milieu interieur*, and of course to Hans Driesch's famous experiment and infamous idea that organisms are self-regulating equipotential systems governed by entelechy, which became the foundation of neovitalism at the beginning of the twentieth century. While the mystery behind the phenomenon of individual development has always been how it is possible that such a complex and fragile process generally leads to a predictable outcome – human eggs develop into recognizable humans and sea urchin eggs into sea urchins – evolution has been perceived as an open-ended process of constant transformation, thus in many ways as the exact opposite of regulation (see Canguilhem 1979). However, development and evolution are more closely linked than one would expect. As the German evolutionary biologist Günter Osche once dryly remarked, evolution cannot put out a sign “Closed Because of Reconstruction.” Indeed, all evolutionary transformations, even though they manifest themselves on a population level, need to materialize within the constraints and possibilities of a functioning developmental system of individual organisms. And the more we learn about the details of these developmental systems – about the intricate regulatory networks and linked pathways that control gene expression and thus differentiation during ontogeny – the more we realize that evolutionary transformations are a consequence of changes in these regulatory systems and other developmental processes. Regulation has thus become a concept that allows us simultaneously to understand the stability of individual development and the possibilities of evolutionary transformations.

But before we continue these discussions of the conceptual structure of evo-devo let us first briefly explore its history (see Laubichler and Maienschein 2007, Amundson 2005, Laubichler 2005, Love and Raff 2003).

1. EVOLUTIONARY DEVELOPMENTAL BIOLOGY:
A NEW SYNTHESIS OR "OLD WINE IN
NEW BOTTLES"?

The study of individual development of organisms has a long history that dates all the way back to Aristotle. Theories of generation, preformism, and epigenesis had a profound impact on the way life was understood as either creative and vital or mechanical as well as on the interpretation of organic forms and their history. And indeed it was in the context of discussions about the development of organic forms that ideas related to the evolutionary history of life first emerged. Darwin, of course, put these questions in focus when he laid out the following problems and observations: (1) Both organisms and species vary. (2) The variation of both organisms and species is not arbitrary, but clustered. In other words, parents and offspring closely resemble each other, but not completely, and different species can be grouped together into higher systematic groups that are united by common features. (3) The specific causes for the similarity and differences between parents and offspring were unknown, but it was clear that these causes had to act in the course of individual development (ontogeny). (4) The principles for grouping individual species together into higher systematic groups were based on comparison and the establishment of homologies. Homologies – the same organs in different individuals irrespective of form and function – were considered the basis for the hierarchical system of classification; it was, however, not always clear how homologies could be established; (5) Embryological observations (*Entwicklungsgeschichte*) had revealed that earlier (less complex) developmental stages of different species more closely resembled each other than did adult stages; (6) The genealogical perspective and the geological record suggested that less complex forms of life emerged earlier in the phylogenetic history (*Stammesgeschichte*) than more complex forms (an argument that had already been made in the context of cultural stages in the history of humankind); (7) It was clear that all explanations as well as the specific details of this history needed to be inferred, often, as with the geological record, from rather incomplete data sets, as direct observation was not an option (Darwin 1859).

Darwin himself, honed by detailed observations of the developmental stages of barnacles, carefully suggested a connection between

ontogeny and phylogeny: "Thus community in the embryonic structure reveals community of descent" (Darwin 1859, 449). Others soon followed suit, exploring how the observable patterns of ontogeny could help to reveal the hidden patterns of phylogeny, most famously Ernst Haeckel, who formulated the biogenetic law, first called that way in 1872. The idea that ontogeny recapitulates phylogeny and the developmental perspective implicit in the biogenetic law also seemed to offer insights into one of the major problems of comparative biology, the establishment of homology relations. A shared developmental history, so Haeckel, should be a solid basis for the assessment of homologies. This later assumption became one of the foundations of evolutionary morphology, a program initiated by Haeckel and his close friend Carl Gegenbaur, which focused on the establishment of a phylogenetic system as the goal of comparative anatomy and embryology (see Nyhart 1995, 2002, Laubichler 2003, Laubichler and Maienschein, 2003).

This new orientation brought about by the emphasis on the relations between ontogeny and phylogeny led to some spectacular insights. In the late 1860s the Russian embryologist Alexander Kowalevsky discovered similarities between the ontogenetic sequences of *Amphioxus* and vertebrates as well as the existence of a *chorda dorsalis* in the larvae of ascidians (Kowalevsky 1867). These discoveries suggested that vertebrates were derived from the larvae of ascidians, a theory that was soon challenged by, among others, Anton Dohrn, the founder of the zoological station in Naples, who proposed an annelid ancestry for vertebrates (Dohrn 1875). This and many similar examples illustrate how, in the decades after the publication of the *Origin of Species*, the scientific problem of ontogeny and phylogeny was primarily determined by the context of evolutionary morphology (phylogeny).

Matters changed around the turn of the twentieth century, when evolutionary morphology gradually disappeared. More experimentally oriented research programs, such as genetics and developmental mechanics and physiology (*Entwicklungsmechanik*), carried the day. *Entwicklungsmechanik* initially emphasized the role of mechanical and physico-chemical causes in explanations of development; only later, in the context of physiological and genetic approaches to development, did evolutionary questions return. These concerns had, in the meantime, been transformed by the

results of experimental genetics. Both Richard Goldschmidt and Alfred Kühn attempted to integrate genetics, development, and evolution; Kühn with his concept of the "Wirkgetriebe der Erbanlagen," a mechanism for realizing hereditary dispositions, and Goldschmidt with his conception of physiological developmental genetics and his discussion of chromosomal rearrangements, macromutations, and "hopeful monsters" (Goldschmidt 1940, Kühn 1955).

The most inclusive research program devoted to questions of ontogeny and phylogeny was directed by Hans Przibram at the Vienna Vivarium, a privately owned and funded research station devoted to experimental biology. Przibram and a group of like-minded and well-to-do scientists established what was at the time the most sophisticated institution for experimental research that focused on the study of development, regeneration, endocrinology, experimental evolution, and the life history of organisms (both plants and animals). In addition, this group was interested in the integration of experimental and theoretical approaches. Their work was, in many ways, the most direct forerunner of current evo-devo. Unfortunately the political turmoil of the 1930s and 1940s put an end to this unique research environment (see, e.g., Przibram 1907).

The two unifying proposals of mid- to late twentieth-century biology were the Modern Synthesis and the emerging molecular biology (e.g., Mayr and Provine 1980, Morange 1998). The former was based on the conceptual integration allowed by the mathematical theory of population genetics, while the latter was based more on a unifying level of analysis and a shared repertoire of experimental approaches than an integrative conceptual framework. While these two approaches and their sometimes acrimonious relations dominated midtwentieth-century biology, experimental embryology, rechristened as developmental biology, continued to flourish in its own scientific niche. But there were always some, such as Conrad Waddington, who emphasized the unity of the evolutionary and developmental research programs. His idea of an epigenetic landscape and the concept of genetic assimilation both represented attempts to incorporate developmental mechanisms into evolutionary explanations (Waddington 1940). By the early 1970s the main focus of developmental biology had turned toward questions of developmental genetics. This was also the time when

a renewed interest in the problem of "ontogeny and phylogeny" began to emerge.

Early contributors to what would later become evo-devo focused on the problem of development and evolution because they were dissatisfied with the explanatory framework of the Modern Synthesis. Several related issues, in particular, were at the heart of their critique. For one, the assumption of the Modern Synthesis that macroevolutionary patterns can be explained by a simple extension of microevolutionary processes was questioned. Palaeontologists, who led this line of attack, focused on two phenomena that they thought could not be reconciled within this framework: (1) The observation that the fossil record of several clades shows periods of rapid evolutionary change followed by extended periods of stasis led to the hypothesis of punctuated equilibrium, and (2) the observation that most conceivable morphological patterns are not realized, that is, that the morphospace is largely empty and that realized morphologies are clustered in certain domains of the morphospace, seemed to support ideas that morphological change is primarily a consequence of developmental processes, such as heterochrony, rather than strictly determined by (incremental) genetic factors (e.g., Eldredge and Gould 1972, Gould 1977).

Another source of dissatisfaction with the Modern Synthesis was the privileged role of adaptation in dominant theories of evolution (see Gould and Lewontin 1979, as the locus classicus for this critique). The adaptationist paradigm was challenged both by molecular biologists (e.g., with the neutral theory of evolution) as well as by evolutionary developmental biologists, who emphasized the role of internal factors in evolution. The most prominent early concepts in this context were the notion of developmental constraint as a limitation on possible phenotypic variation and therefore on adaptation and Rupert Riedl's idea of "burden," which postulates an internal, in addition to the external and environmentally induced, selection pressure (Riedl 1975, Maynard-Smith et al. 1985). The internal conditions, which act as a second (or rather first) selective environment, are those of the developing system. In the context of Riedl's theory these internal factors, or system conditions, as he calls them, can explain both the evolvability as well as the hierarchical organization of organismal forms (Riedl 1975, Wagner and Laubichler 2004).

By the mid-1980s a consensus had been reached that the prevailing version of evolutionary theory needed to be reformed. However, even though there was general agreement that development needed to be part of evolutionary theory, there was far less agreement about the actual research agendas or about the best strategies to accomplish this desired new synthesis. These centrifugal tendencies only grew stronger after the discovery of the conserved sequences of Homeobox genes provided a major boost to the developmental genetic version of evo-devo.

This plurality of approaches to the problem of ontogeny and phylogeny, which continues to this day, despite growing attempts to establish a genuine new "synthesis" of evo-devo, is also reflected in its current fragmented structure. An integrative framework that would unite all these different evo-devo applications within a genuine new "synthesis" has, as of yet, not emerged. What we can observe, however, is a clustering of research questions around two or three main emphases, such as "evo-devo," "devo-evo," and "developmental evolution" (see Hall 2000, Wagner et al. 2000, Müller 2005).

2. RESEARCH PROGRAMS WITHIN EVO-DEVO

As we have seen in this brief historical overview, present-day evo-devo has many different roots. Correspondingly, there are also several distinct research programs currently pursued under the banner of evo-devo. Some of those clearly overlap, and collectively these different research programs illustrate the methodological pluralism that is characteristic of evo-devo. This multitude of approaches also helps to understand the current prominence of evo-devo-related research within organismal biology. However, the same diversity that makes evo-devo research so productive in many ways also provides a formidable challenge to any attempts to arrive at a synthesis of different perspectives (more on that later). The main research programs within evo-devo are the following (see also Laubichler 2005, Müller 2005):

1. *The comparative program.* Comparative research is one of the oldest paradigms within biology. It continues to raise important questions and provides the foundation of all further investigations.

Today comparative research covers many different levels of biological organization, from morphology and anatomy to embryology and genomics. In the context of the latter the emphasis has now shifted from simple sequence comparison to comparison of gene expression patterns and gene products and their interactions, thus allowing a comparative study of developmental sequences at high resolution. The comparative program is also important for evo-devo in that it provides us with detailed phylogenies. These are important in assessing any number of genuine evo-devo questions, such as hypotheses about evolutionary transformations or homology.

2. *The experimental program.* The experimental program is a continuation of the venerable tradition of experimental embryology and developmental physiology that dominated organismal biology during the first decades of the twentieth century. The focus of these experimental approaches lies in the elucidation of the mechanisms of development. Even though most experimental research in developmental biology today focuses on the role of genes in development, there is also an increasing awareness of the importance of epigenetic and environmental factors in morphogenesis and evolution. We have already seen that regulation has become one of the central concepts in describing both developmental systems and their evolution. Epigenetic factors, such as differential methylation patterns, genomic imprinting, posttranscriptional control, and RNA editing, as well as biophysical properties of cells and tissues, geometrical patterns of self-organizing systems, and environmental factors such as temperature, all contribute to the regulatory machinery of developmental systems and their evolution. In manipulating the parameters of developing systems the experimental program within evo-devo has produced some interesting results. Among those are the recreation of ancestral morphological patterns in limbs or the elucidation of the rules of digit reduction (Alberch and Gale 1983, Müller 1989). In both cases morphological transformations that closely resemble actual evolutionary transformations were accomplished by means of experimental manipulation of nongenetic parts of the developmental systems, such as constricting the size or manipulating the geometry of limb buds. These approaches contribute greatly to our understanding of the patterns and processes of evolutionary transformations.

3. *The program of evolutionary developmental genetics.* The focus of this research program is on the genetic components of developmental systems and their interactions. In many ways evolutionary developmental genetics is the most visible part of current evo-devo. The discoveries first of *Hox* genes and of other transcription factors that together make up the regulatory gene networks controlling the expression of genes and the differentiation of embryonic anlagen and then of the high degrees of conservation of these very genes have received the most attention. These discoveries also contributed (falsely, as we have seen) to the impression that evo-devo began with the *Hox* story. Among the ideas that emerged in the context of these investigations are the notion of a *genetic toolkit for development* – a set of regulatory elements that are involved in the development of the main features of animal bodies, such as segmental patterning and axis formation – and the proposal to reconstruct a so-called *Urbilateria* as the ancestral condition of all higher animals. The latter combines the insights of the comparative program with the discovery of the genetic toolkit for development (see Carroll et al. 2005 for an overview).

4. *The theoretical and computational program within evo-devo.* Evo-devo has also triggered a lot of theoretical research, especially during the last decades. This part of evo-devo is only becoming more prominent as newly developed formal and mathematical approaches begin to add more rigor to long-standing conceptual ideas. The theoretical program is especially important as it has the potential to provide conceptual unification to otherwise diverse experimental approaches (see later discussion). It also represents a disciplinary counterweight to the program in evolutionary developmental genetics. While the latter is largely dominated by researchers trained in molecular or developmental biology, the former is the domain of evolutionary biologists, who often refer to their approach as developmental evolution or devo-evo. In this context Günter Wagner, a trained evolutionary biologist and editor-in-chief of the *Journal of Experimental Zoology, Part B: Molecular and Developmental Evolution*, one of the leading evo-devo journals, always speaks of developmental evolution. These differences are more than just semantics, as they also correspond to different epistemological convictions and explanatory frameworks. Simply put, developmental biologists tend to be more interested in

structural and typological explanations based on molecular and cellular mechanisms, while evolutionary biologists focus more on dynamic processes on a population and species level (see also Hall 2000 for a discussion about the differences of evo-devo and devo-evo and Amundson 2005 for a detailed account of the different epistemological and explanatory frameworks). The integration of these two approaches is anything but straightforward, although recent theoretical developments that include work on genotype-phenotype maps including questions of how best to characterize phenotype space and morphospace, theoretical and empirical analyses of modularity and robustness, phenotypic plasticity, life history, as well as evolvability, all contribute to a framework that might just prove flexible enough to integrate the different empirical and theoretical traditions (see Callebaut and Raskin 2005, Schlosser and Wagner 2004, West Eberhard 2003, Müller and Newman 2003, Hall and Olson 2003). Theoretical work is also greatly aided by new developments in computational methods and representations. The databases of the various genome projects have been indispensable for identifying developmentally active genes and establishing their evolutionary history. As functional annotations of genes in these databases increase and gene ontologies become more sophisticated, it will soon be possible to extract the kind of information about developmental genes that is necessary for a more detailed understanding of the evolution of developmental systems. What we have learned for *Hox* and related genes, how their expression domains shift in different species, and how this correlated with morphological changes, for instance, or what the consequences of certain duplication events have been, will soon be available for a large number of transcription factors, signaling genes, and receptor proteins. In addition, computational reconstructions of gene expression patterns in developing embryos will organize data in a way that will greatly aid mathematical modeling of developmental systems. One example of this approach is Adam Wilkins's analysis of the evolution of genetic pathways in developmental systems, which suggests that certain changes, such as upstream addition of control elements, are more likely than others (Wilkins 2002). To sum up, the theoretical and computational program within evo-devo is about to get a great boost from the increasing success of experimental approaches. Interesting times thus lie ahead.

Analyzing the different research programs within evo-devo is just one way to capture the diversity, excitement, and potential of the field. Another way to help us understand why evo-devo is such a central part of current organismal biology is to investigate some of the concrete research problems that make up the core of present day evo-devo.

3. RESEARCH QUESTIONS IN EVO-DEVO

There are many specific questions that are currently investigated within the framework of evo-devo so we will have to be selective here. But generally most of the individual problems will be connected to one of six areas of research (Laubichler 2005, Müller 2005).

1. *The origin and evolution of developmental systems.* This question focuses on the evolutionary transformation of the developmental systems themselves. Developmental systems, as any other character of organisms, undergo evolutionary transformations. Research in this area reveals the modular architecture of developmental systems and investigates their robustness and how different developmental modules are combined and regulated.

2. *The problem of homology.* The problem of homology is one of the central questions of all of biology. It is often separated in a historical homology concept, used mainly in phylogenetic analyses, which describes the distribution of homologues, and a biological homology concept, which attempts to explain the existence of homologies in the first place. An evo-devo framework employs both notions of homology and tries to integrate them.

3. *The genotype-phenotype relation.* Mapping the genotype onto the phenotype has emerged as a main problem within evolutionary and quantitative genetics during the last decades. It is also the question that most directly involves developmental mechanisms. For a long time population genetic models assumed that development does not affect the mapping of genotypic onto phenotypic variation in any important way – development was thus treated as a constant. As this position can no longer be upheld, investigations into the formal properties of the genotype-phenotype map have become a major focus within evo-devo.

4. *The patterns of phenotypic variation.* It has long been known that patterns of phenotypic variation are highly clustered and

constrained. Explanations of this phenomenon have always included references to the developmental system, mostly in the form of developmental constraints that limit the possible phenotypic variants. Recently it has also become clear that the evolvability of certain lineages also crucially depends on the existence of developmental constraints. This question is thus also a main concern for evo-devo researchers.

5. *The role of the environment in development and evolution.* More recently environmental factors have also been incorporated into the evo-devo research program. The more we learn about the molecular mechanisms, such as DNA methylation or endocrine disruption, through which the environment can influence the phenotypic expression, the more it becomes obvious that the environment has to become a larger part of explanations within evo-devo.

6. *The origin of evolutionary novelties.* Explaining the origin of novel phenotypic traits has been one of the major challenges of evolutionary biology. As evo-devo offers the first integrated perspective that has the potential to comprehensively address this problem, we will discuss this question in more detail.

4. THE PROBLEM OF EVOLUTIONARY NOVELTIES

The major challenge for evolutionary biology is to explain the origin of complex novel structures and functions. Darwin already struggled with this problem in the *Origin of Species*. "What good is 5% of an eye?" is an often repeated question and even today the idea of "irreducible complexity" is taken as evidence for "intelligent design" and for the obvious shortcomings of the neo-Darwinian paradigm based on "an unguided, unplanned process of random variation and natural selection," which simply cannot be true. Part of the problem is that proponents of intelligent design are consciously misrepresenting evolutionary biology as neo-Darwinism and are systematically ignoring all the evidence that has accumulated over the last twenty-some years in the context of evo-devo, evidence that helps us understand how something new can actually emerge in the course of evolution. But, as the case of intelligent design also shows, evo-devo and especially what it can teach us about the origin of evolutionary innovations are of more than just academic interest (see also Kirschner and Gerhart 2005).

Since the first draft sequence of the human genome was completed in 2001, some of the simplistic assumptions about the relationship between genotype and phenotype have been challenged by the realization that the actual number of human genes is relatively low, only around 30,000, and that most of these genes (close to 19,000) are already present in tiny nematode worms, such as *C. elegans*. Many of the important regulatory genes and transcription factors, such as the *Hox* genes, are also highly conserved between lineages that have been separated by hundreds of millions of years. Novel features are thus not just a consequence of new genes or even new versions of old genes.

What then accounts for the obvious phenotypic differences between groups of organisms and for the emergence of novel structures in the course of evolution? The short answer to this question is that changes in the developmental systems of these organisms and more specifically changes in the regulatory networks of genes are responsible for these differences. In other words, the same mechanisms that lead to differentiation of cells in the course of individual development (ontogeny) also account for emerging differences in the course of evolution (phylogeny). Intuitively this makes sense. All phenotypic differences, whether they are just variations of a common theme or something radically different, emerge during the development of individual organisms. Developmental processes will thus always be the immediate or proximate causes of phenotypic variation. Still several questions remain: Exactly how do developmental mechanisms contribute to phenotypic changes, and how can we integrate such developmental explanations into the theoretical framework of evolutionary biology?

The key idea that helps us understand these issues is the concept of regulation. Development itself is a highly regulated process. How would it otherwise be possible that despite constant environmental disturbances the outcomes of development are generally predictable such that humans give birth to humans and sea urchin eggs develop into sea urchins? While developmental biology focuses on individual developmental sequences describing the transformation from simple (a fertilized egg) to complex (an adult organism) through the differentiation of cells and the emergence of anatomical and histological structures, evo-devo tries to understand how in the

course of evolution something new can emerge within these regulated developmental sequences. But before we can address potential explanations of such evolutionary novelties we first have to define the problem more precisely.

Addressing the problem of evolutionary innovations requires us first to define clearly what we mean by "novelties" and, second, to develop a set of causal hypotheses that will allow us to identify the developmental changes involved in the emergence of an evolutionary novelty. In their seminal analysis of the problem Müller and Wagner defined a morphological novelty as "a structure that is neither homologous to any structure in the ancestral species, nor homonomous to any other structure of the same organism" (Müller and Wagner 1991, 243). While this rather general definition still leaves open many details, it does have one practical implication. The problem of identifying novelties is squarely placed within the comparative program of evo-devo as their recognition depends on both a good phylogeny and a detailed assessment of homology.

Setting aside, for the moment, many of the practical problems connected with recognizing novelties (which are similar to the problems of assessing homology) we can identify some of the steps required for establishing a causal hypothesis about the origin of evolutionary novelties within the context of evo-devo. The first question that needs to be addressed is, What specific developmental mechanisms are responsible for a new derived character state that has been identified as an evolutionary novelty? Answering this question requires the detailed analysis of the developmental mechanisms that generate a specific phenotypic character. It is thus part of the experimental program of evo-devo. The second question builds on this analysis: Did the developmental mechanisms that are responsible for the derived character state originate at the same time as this character state? This is already a difficult question that requires us to compare the developmental mechanisms of ancestral and derived character states. In many cases this will not be possible, as it is impossible to reconstruct the exact ancestral condition of developmental processes, especially if the transformation in question happened hundreds of millions of years ago. The same problems also apply to the third and fourth questions: What were the exact developmental mechanisms responsible for the initial changes in the character state? Are the observed genetic differences between

these two developmental systems sufficient to account for the observed phenotypic differences? These last two questions focus on the mechanistic details of the changes in the developmental system and the extent to which observable genetic changes provide a complete explanation of evolutionary transformations (Wagner et al. 2000).

We still face many practical difficulties with most cases of evolutionary novelties currently under investigation. Part of the problem can be attributed to the selection of examples and model organisms, which tend to focus on major morphological transformations, such as the fin-limb transition in early vertebrates. However, there are some model systems that do allow us to address questions about the origin of evolutionary novelties experimentally as well as theoretically. For example, social insects display a remarkable diversity in behavior ranging from solitary to eusocial. For many of these species we know their phylogeny, genetics, developmental mechanism, as well as their physiological and behavioral repertoire. And we can manipulate them experimentally in the lab, in several cases actually inducing novel types of social behavior among solitary species. Social insects are therefore an ideal model system for the study of evolutionary novelties. This work is only just beginning, but we can expect that it will lead to many important insights into the problem of evolutionary novelties.

Another issue that needs to be mentioned here is whether genetic differences (including differences in the genetic parts of regulatory networks) alone provide a sufficient explanation for the origin of evolutionary novelties. Our fourth question specifically addresses this issue. By now we have ample evidence that epigenetic and environmental factors, which are part of the developmental system in many organisms, play an important part in the origin of evolutionary novelties, especially during the initial phases of character transformation. On the basis of such observations Müller and Newman have suggested a three-step model for the origin of evolutionary novelties that assumes that the initial emergence of new characters is often caused by epigenetic and environmental mechanisms that are later stabilized by associated genetic changes (Müller and Newman 1999, 2003). While this is still a rather controversial idea, it can be tested, especially with social insects, among which many emergent colony-level traits, such as division of labor

and caste distribution, are often a consequence of within-colony interactions, rather than simple mutations.

5. EVO-DEVO AND THE PROBLEM OF INTERDISCIPLINARY INTEGRATION

Conceptual integration of rather diverse research paradigms is the main challenge that evo-devo currently faces. Therefore, it can easily be argued that the future of evo-devo as a true interdisciplinary synthesis will depend more on theoretical advances than on additional experimental data. As we all know, appearances can be deceiving, and the deluge of exciting experimental results over the last two decades has in many ways hidden an underlying conceptual tension that will have to be resolved for evo-devo to succeed. In his recent book Ron Amundson pointed out in great detail how developmental and evolutionary explanations are based on rather different epistemological foundations (Amundson 2005). The former are rooted in what Amundson refers to as a structuralist paradigm that is based on a causal understanding of general molecular and cellular mechanisms, such as molecular gradients, cell-surface interactions, and cell-cell signaling, while the latter are predicated on a mathematical formulation of underlying population-level dynamics, such as the replicator equation, the generalized selection equations, or stochastic processes, such as random genetic drift.

The earlier success of the Modern Synthesis of the 1930s and 1940s, which is often held up as a model for an emerging evo-devo synthesis, was based on matching patterns – of the transmission of genetic information, of speciation and adaptation, and of the fossil record – with dynamical processes within populations (see Mayr and Provine 1980 for an overview of issues related to the Modern Synthesis). Something similar will have to be accomplished for evo-devo. Observed patterns of morphological and behavioral evolution will have to be matched with the possibilities and constraints of developmental systems and the dynamical processes within populations. Such integration will depend on a conceptual framework and associated dynamical models that adequately represent both the actual phenomena to be explained (patterns of morphological and behavioral evolution) as well as the underlying dynamics that

generated them (see also Wagner et al. 2000, Wagner's series of editorials in *Molecular and Developmental Evolution* [2000, 2001], Wagner and Larsson 2003, Laubichler 2005).

What form could such integration take? As we have seen in our brief historical overview, developmental mechanisms have always featured prominently in attempts to explain patterns of phenotypic diversity and transformation. Whether these were conceptualized as "laws of variation" (Darwin), "recapitulation" and "terminal addition" (Haeckel), "homeotic mutations" and "hopeful monsters" (Goldschmidt), or "genetic assimilation" (Waddington), the general argument has always been the same: phenotypic changes have to arise during ontogeny; therefore, changes in ontogeny will have to be responsible for observed patterns of phenotypic evolution. The details and specific concerns of these explanations differed, of course, but this variation does not detract from their underlying similarity. Evo-devo falls within the same explanatory paradigm, but it also differs in several important ways. For one, our current understanding of the molecular, cellular, genetic, and epigenetic mechanisms of development is much more detailed and our abilities to manipulate developmental systems experimentally have advanced rather dramatically. This increased understanding of developmental mechanisms has led to a more refined conceptual representation of development that is no longer based on simple mechanical forces, such as the actions of a somewhat mysterious "organizer," or gradients of molecules. Our current understanding of developmental differentiation includes complex causal pathways and interactions between genetic and epigenetic regulatory networks.

We have already indicated several times that regulation has become one of the central concepts in both developmental biology and evo-devo. Indeed, many scientists argue that modifications in the regulatory networks – so-called regulatory evolution – can account for the observed phenotypic transformations (see, for example, Carroll et al. 2005, Davidson 2001, 2006, Wilkins 2002). While changes in the regulatory networks are certainly an important part of the explanation of patterns of phenotypic diversity, our explanatory schema will have to be expanded. First we will have to establish a more adequate conceptual framework for what we want to explain. Evolutionary novelties are a prominent part of the

evo-devo explanandum, but related concepts such as facilitated variation, developmental constraints, modularity, robustness, and evolvability, all concepts that have recently been analyzed within the context of evo-devo, will have to be fully integrated into its conceptual framework (see, for instance, Callebaut and Gutman 2005, Kirschner and Gerhart 2005, Maynard Smith et al. 1985, Schlosser and Wagner 2004). These concepts are also tied into the different research programs within evo-devo, A detailed epistemological analysis, of the sort provided by Ron Amundson, of these programs and their underlying assumptions is therefore crucial for the future of evo-devo as a synthetic enterprise.

But before we attempt such a synthesis we should also consider what we mean by synthesis, what exactly should be synthesized, and what we expect from such a synthesis. The Modern Synthesis was successful because, after an initial phase of intense discussions, it emerged with a clear explanatory agenda – how population genetic models can be used to explain adaptation and speciation. And even though these simple principles or their underlying assumptions were almost never “true” for any real case, they nevertheless anchored a very productive experimental and theoretical research enterprise, which ultimately led to our current period of methodological and conceptual pluralism. If we take the historical lesson of the Modern Synthesis to be that the role of a synthesis is to provide a conceptual foundation for different research programs that will ultimately explore the fuzzy edges and areas beyond the core of the synthesis, then we advocate an open conception of synthesis rather than a closed view based on integration of existing paradigms.

Seen that way the role of an evo-devo synthesis would be to provide a set of core concepts and assumptions that allow further research, realizing that this research will eventually transcend the explanatory framework of the current synthesis. How would such an open-ended synthesis look? It is probably too early to tell, but it will have to be based on a conceptual structure that allows the integration of developmental mechanisms into evolutionary explanations at a higher level of resolution than the current ideas about regulatory evolution and the evolution of the genetic toolkit suggest. It will also have to develop a more comprehensive conception of mechanistic causes for both development and evolution that includes

genetic, epigenetic, and environmental factors. And it will have to develop a set of paradigmatic model systems that will allow us to study these questions. As we have seen, there are some very promising new model systems currently developed that might just be the right tool for the job. In any case, these are exciting times for both scientists and philosophers to collaborate on some of the most fundamental problems of biology.